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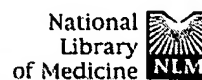
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#8	Search <b>HCV cell culture</b> Limits: <b>Publication Date to 2000/11/07</b>	17:57:09	<u>67</u>
#7	Search <b>transfection HCV</b> Limits: <b>Publication Date to 2000/11/07</b>	17:56:47	<u>131</u>
#5	Search <b>subgenomic HCV</b> Limits: <b>Publication Date to 2000/11/07</b>	17:55:22	<u>17</u>
#2	Search <b>HCV replicon</b> Field: <b>All Fields</b> , Limits: <b>Publication Date to 2000/11/07</b>	17:54:00	<u>3</u>
#1	Search <b>HCV replicon</b>	17:53:41	<u>77</u>

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PubMed	Nucleotide	Protein	Genome	Structure	PMC	Taxonomy	OMIM	Books	
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- Search History will be lost after one hour of inactivity.
- To combine searches use # before search number, e.g., #2 AND #6.
- Search numbers may not be continuous; all searches are represented.

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Search	Most Recent Queries	Time	Result
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#2	Search viral like partichel and HCV	12:38:01	<u>0</u>
#1	Search Yi M HCV	12:37:06	<u>6</u>

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NEWS	8	Sep 16	Experimental properties added to the REGISTRY file
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NEWS	12	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
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NEWS	17	Dec 17	TOXCENTER enhanced with additional content
NEWS	18	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS	19	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS	20	Feb 13	CANCERLIT is no longer being updated
NEWS	21	Feb 24	METADEx enhancements
NEWS	22	Feb 24	PCTGEN now available on STN
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NEWS	24	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS	25	Feb 26	PCTFULL now contains images
NEWS	26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS	27	Mar 20	EVENTLINE will be removed from STN
NEWS	28	Mar 24	PATDPAFULL now available on STN
NEWS	29	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS	30	Apr 11	Display formats in DGENE enhanced
NEWS	31	Apr 14	MEDLINE Reload
NEWS	32	Apr 17	Polymer searching in REGISTRY enhanced
NEWS	33	Apr 21	Indexing from 1947 to 1956 being added to records in CA/CAPLUS
NEWS	34	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX
NEWS	35	Apr 28	RDISCLOSURE now available on STN
NEWS	36	May 05	Pharmacokinetic information and systematic chemical names added to PHAR
NEWS	37	May 15	MEDLINE file segment of TOXCENTER reloaded
NEWS	38	May 15	Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS	39	May 16	CHEMREACT will be removed from STN
NEWS	40	May 19	Simultaneous left and right truncation added to WSCA

NEWS 41 May 19 RAPRA enhanced with new search field, simultaneous left and right truncation

NEWS EXPRESS April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT  
MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),  
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=> file caplus

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FILE 'CAPLUS' ENTERED AT 17:30:09 ON 30 MAY 2003

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FILE COVERS 1907 - 30 May 2003 VOL 138 ISS 23

FILE LAST UPDATED: 29 May 2003 (20030529/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> HCV (w) replicon

6501 HCV

15 HCVS

6504 HCV

(HCV OR HCVS)

2579 REPLICON

1325 REPLICONS

```

    3201 REPLICON
        (REPLICON OR REPLICONS)
L1      43 HCV (W) REPLICON

=> T7 (w) promoter and L1
    8520 T7
    134658 PROMOTER
    46238 PROMOTERS
    152997 PROMOTER
        (PROMOTER OR PROMOTERS)
    1605 T7 (W) PROMOTER
L2      0 T7 (W) PROMOTER AND L1

=> T7 and L1
    8520 T7
L3      1 T7 AND L1

=> recombinant and L1
    144584 RECOMBINANT
    6051 RECOMBINANTS
    147921 RECOMBINANT
        (RECOMBINANT OR RECOMBINANTS)
L4      5 RECOMBINANT AND L1

=> neo and L1
    7687 NEO
    31 NEOS
    7714 NEO
        (NEO OR NEOS)
L5      3 NEO AND L1

=> NTR and L1
    762 NTR
    79 NTRS
    798 NTR
        (NTR OR NTRS)
L6      4 NTR AND L1

=> Huh-7 and L1
    573 HUH
    1 HUHS
    574 HUH
        (HUH OR HUHS)
    2347077 7
    484 HUH-7
        (HUH(W) 7)
L7      14 HUH-7 AND L1

=> cDNA and L1
    149797 CDNA
    23218 CDNAS
    156505 CDNA
        (CDNA OR CDNAS)
L8      3 CDNA AND L1

=> HCV (w) cDNA
    6501 HCV
    15 HCVS
    6504 HCV
        (HCV OR HCVS)

```

149797 CDNA  
23218 CDNAS  
156505 CDNA  
(CDNA OR CDNAS)

L9 108 HCV (W) CDNA

=> transfection and L9

30420 TRANSFECTION  
1489 TRANSFECTIONS  
31447 TRANSFECTION  
(TRANSFECTION OR TRANSFECTIONS)

L10 7 TRANSFECTION AND L9

=> Huh-7 and L9

573 HUH  
1 HUHS  
574 HUH  
(HUH OR HUHS)

2347077 7  
484 HUH-7  
(HUH(W) 7)

L11 4 HUH-7 AND L9

=> DIS L11 1- IBIB ABS

YOU HAVE REQUESTED DATA FROM 4 ANSWERS - CONTINUE? Y/(N):Y  
THE ESTIMATED COST FOR THIS REQUEST IS 9.66 U.S. DOLLARS  
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L11 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:716438 CAPLUS

DOCUMENT NUMBER: 137:227663

TITLE: Hepatitis C virus (HCV) cDNA-based  
hepatocyte cell culture system for synthesis of  
infectious HCV, and uses for antiviral screening

INVENTOR(S): Dasgupta, Asim; Koka, Prasad S.

PATENT ASSIGNEE(S): The Regents of the University of California, USA

SOURCE: PCT Int. Appl., 42 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002072776	A2	20020919	WO 2002-US7516	20020311
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
US 2002197277	A1	20021226	US 2002-96039	20020311

PRIORITY APPLN. INFO.:

US 2001-274709P P 20010309

AB The present invention presents a method of synthesizing infectious hepatitis C virus (HCV) by transfecting hepatocyte cells with a gene

encoding HCV and then exposing uninfected cells to the HCV to form addnl. HCV. The invention relates to a **HCV cDNA**-based culture system capable of synthesis of infectious HCV in cell culture and cell-to-cell spread of the virus. The expression of T7 RNA polymerase in the cytoplasm was used to transcribe the **HCV cDNA** under the T7 promoter to generate high quantities of HCV RNA. The viral RNA proved to be translated to produce viral structural (core, E1, E2 and p7) and nonstructural (NS2, NS3, NS4A and B, NS5A and B) proteins. Viral RNA replication directed by the RNA-dependent RNA polymerase (NS5B) would then occur. Progeny virions were made and secreted into the tissue culture media, and infection of neighboring cells resulting in cell-to-cell spread of virus was demonstrated. The invention also relates to a method of measuring the level of HCV infection in a hepatocyte cell. A method for identifying a modulator of HCV activity is also presented, and a method for modulating HCV activity. The invention provides a reliable system for both genetic anal. of the viral genome and for the development of novel antiviral strategies.

L11 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:879072 CAPLUS

DOCUMENT NUMBER: 136:245404

TITLE: Hepatitis C Viral Proteins Affect Cell Viability and Membrane Permeability

AUTHOR(S): Kalkeri, Gururaj; Khalap, Nutan; Akhter, Shamim; Garry, Robert F.; Fermin, Cesar D.; Dash, Srikanta

CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, Tulane University Health Science Center, New Orleans, LA, 70112, USA

SOURCE: Experimental and Molecular Pathology (2001), 71(3), 194-208

CODEN: EXMPA6; ISSN: 0014-4800

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To det. the effect of hepatitis C virus (HCV) proteins on cell growth, Huh-7 cells were transfected with a full-length HCV cDNA (pMO9.6-T7 Rz) clone and HCV proteins were expressed using a replication-defective adenovirus that encodes the gene for the T7 RNA polymerase. Expression of HCV proteins from this full-length clone resulted in redn. in viability of transfected cells as measured by trypan blue viability assay. For identification and sepn. of cells expressing hepatitis C virus proteins by fluorescence microscopy and

flow cytometry, GFP was cloned in the HCV full-length clone. Cells transfected with the HCV-GFP chimera clone produced high levels of accurately processed structural and nonstructural proteins similar to those of the HCV full-length clone, which could be detected by Western blot anal. Cells expressing all HCV proteins lost membrane permeability and underwent apoptotic cell death, indicated by the appearance of a sub-G0 peak in cell cycle anal., DNA fragmentation in a TUNEL assay, and microscopic detection of nuclear condensation. Using double-channel flow anal. we confirmed that high-level expression of HCV proteins affected membrane permeability and cell survival. These results suggest that expression of all structural and nonstructural proteins from HCV cDNA in hepatic cells induces apoptotic cell death, which might be an important event in chronic hepatitis infection in humans. (c) 2001 Academic Press.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L11 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:155647 CAPLUS

DOCUMENT NUMBER: 131:68779

TITLE: Expression of Hepatitis C Virus cDNA in Human Hepatoma

AUTHOR(S): Cell Line Mediated by a Hybrid Baculovirus-HCV Vector  
Fipaldini, Cristina; Bellei, Barbara; La Monica, Nicola

CORPORATE SOURCE: IRBM "P. Angeletti", Pomezia, 00040, Italy

SOURCE: Virology (1999), 255(2), 302-311

CODEN: VIRLAX; ISSN: 0042-6822

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Although great progress has been made in the characterization of the biochem. and biol. features of hepatitis C virus (HCV) gene expression, the elucidation of the HCV life cycle and the evaluation of novel antiviral strategies have been hindered by the lack of a suitable cell culture system. In this context, the development of an efficient **HCV cDNA** delivery method would contribute to the understanding of HCV replication. To assess the functionality of baculovirus mediated gene delivery for HCV expression, we have constructed

recombinant baculoviruses encoding **HCV cDNA** under the control of the cytomegalovirus promoter. Transduction of the human hepatoma cell line Huh-7 with Bac-HCV vectors was efficient and **HCV cDNA** expression was enhanced by treatment of the infected cells with dexamethasone. HCV structural and nonstructural polypeptides were processed correctly and were found to localize in the cytoplasm in a pattern characteristic of the endoplasmic reticulum. The expression of the HCV proteins was detected for 49 days after infection. Thus, these results indicate that the recombinant Bac-HCV vectors are a useful tool for the delivery of **HCV cDNA** and can facilitate the anal. of structural and functional properties of the HCV proteins. In addn., the Bac-HCV vectors can provide

important information on the evaluation of novel anti-HCV antiviral strategies. (c) 1999 Academic Press.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS

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FORMAT

L11 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:271824 CAPLUS

DOCUMENT NUMBER: 122:76311

TITLE: Transfection of a differentiated human hepatoma cell line (Huh7) with in vitro-transcribed hepatitis C virus (HCV) RNA and establishment of a long-term culture persistently infected with HCV

AUTHOR(S): Yoo, Byoung J.; Selby, Mark J.; Choe, Joonho; Suh, Byung S.; Choi, Steven H.; Joh, Jean S.; Nuovo, Gerald

J.; Lee, Hyo-Suk; Houghton, Michael; Han, Jang H.

CORPORATE SOURCE: Chiron Corp., Emeryville, CA, 94608, USA

SOURCE: Journal of Virology (1995), 69(1), 32-8

CODEN: JOVIAM; ISSN: 0022-538X



PUBLISHER: American Society for Microbiology  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB T7 RNA polymerase transcripts of a putative full-length cDNA clone of hepatitis C virus type 1 (HCV-1) were used to transfect a differentiated human hepatoma cell line, Huh7. The transfected genome replicated in cells, as evidenced by the appearance of progeny HCV RNA, detection of neg.-strand viral RNA, and incorporation of [3H]uridine into the viral genome. Incubation of naive Huh7 cells with conditioned medium from transfected cells resulted in a new HCV infection, suggesting the prodn. of biol. active virus in the inoculum. Maintenance of the transfected cells under serum-free culture conditions resulted in the selection of persistently infected cells which displayed a distinctive cellular morphol. This is the first demonstration that HCV RNA produced from cloned HCV cDNA is infectious and replication competent. This approach should provide a valuable system for studying HCV replication, persistence, and pathogenicity.

=> DIS L10 1- IBIB ABS

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DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L10 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:716438 CAPLUS

DOCUMENT NUMBER: 137:227663

TITLE: Hepatitis C virus (HCV) cDNA-based  
hepatocyte cell culture system for synthesis of  
infectious HCV, and uses for antiviral screening

INVENTOR(S): Dasgupta, Asim; Koka, Prasad S.

PATENT ASSIGNEE(S): The Regents of the University of California, USA

SOURCE: PCT Int. Appl., 42 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002072776	A2	20020919	WO 2002-US7516	20020311
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
US 2002197277	A1	20021226	US 2002-96039	20020311

PRIORITY APPLN. INFO.: US 2001-274709P P 20010309

AB The present invention presents a method of synthesizing infectious hepatitis C virus (HCV) by transfecting hepatocyte cells with a gene encoding HCV and then exposing uninfected cells to the HCV to form addnl. HCV. The invention relates to a HCV cDNA-based culture system capable of synthesis of infectious HCV in cell culture and cell-to-cell spread of the virus. The expression of T7 RNA polymerase in

the cytoplasm was used to transcribe the HCV cDNA under the T7 promoter to generate high quantities of HCV RNA. The viral RNA proved to be translated to produce viral structural (core, E1, E2 and p7) and nonstructural (NS2, NS3, NS4A and B, NS5A and B) proteins. Viral RNA replication directed by the RNA-dependent RNA polymerase (NS5B) would then occur. Progeny virions were made and secreted into the tissue culture media, and infection of neighboring cells resulting in cell-to-cell spread of virus was demonstrated. The invention also

relates

to a method of measuring the level of HCV infection in a hepatocyte cell. A method for identifying a modulator of HCV activity is also presented, and a method for modulating HCV activity. The invention provides a reliable system for both genetic anal. of the viral genome and for the development of novel antiviral strategies.

L10 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:275725 CAPLUS

DOCUMENT NUMBER: 136:274236

TITLE: Hepatitis C virus infection of small animals by genomic RNA administration into liver and use in drug screening

INVENTOR(S): Kohara, Michinori; Katsume, Tomoo

PATENT ASSIGNEE(S): Tokyo Metropolitan Organization for Medical Research, Japan; Chugai Seiyaku Kabushiki Kaisha

SOURCE: PCT Int. Appl., 30 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002028174	A1	20020411	WO 2001-JP7498	20010830
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001082560	A5	20020415	AU 2001-82560	20010830
PRIORITY APPLN. INFO.:			JP 2000-303374	A 20001003
			WO 2001-JP7498	W 20010830
AB A methods for efficient infection of small animals with hepatitis C virus (HCV) by administering the genomic RNA of HCV into the liver of the small animal, or administering a culture supernatant of animal cells having a vector contg. cDNA corresponding to the genomic RNA of HCV to the small animal; is disclosed. A small animal infected with HCV by such a method; and a method of screening a remedy for HCV-assocd. diseases or a HCV growth inhibitor by using the yield of the virus as an indication, are claimed. Infection of tree shrews (tupaia) with HCV genomic RNA by administering into the liver, and administering a culture supernatant of IMY-N9 cells transfected with plasmid vector pCALN/HCV-RBZ contg. full length of cDNA for the genome of HCV, is described. Although hepatitis C virus (HCV) infection can be reproduced in chimpanzees, these animals are rare and expensive. Tree shrews (tupaia) are small animals, closely related to primates, which adapt easily to a lab. environment.				

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT

L10 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:706406 CAPLUS

DOCUMENT NUMBER: 136:245390

TITLE: Transmission of HCV to a chimpanzee using virus particles produced in an RNA-transfected HepG2 cell culture

AUTHOR(S): Dash, Srikanta; Kalkeri, Gururaj; McClure, Hazel M.; Garry, Robert F.; Clejan, Sanda; Thung, Swan N.; Murthy, Krishna K.

CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, Tulane University Health Science Center, New Orleans, LA, USA

SOURCE: Journal of Medical Virology (2001), 65(2), 276-281  
CODEN: JMVIDB; ISSN: 0146-6615

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB It was demonstrated previously that HepG2 cells produce neg. strand RNA and virus-like particles after **transfection** with RNA transcribed from a full-length hepatitis C virus (HCV) cDNA clone [Dash et al. (1997) American Journal of Pathol., 151:363-373]. To det.

in vivo infectivity of these in vitro synthesized viral particles, a chimpanzee was inoculated i.v. with HCV derived from HepG2 cells. The infected chimpanzee was examd. serially for elevation of liver enzymes, for the presence of HCV RNA in the serum by reverse transcription nested polymerase chain reaction (RT-PCR), anti-HCV antibodies in the serum, and inflammation in the liver. The chimpanzee developed elevated levels of liver enzymes after the second week, but the levels fluctuated over a 10-wk period. HCV RNA was detected in the serum of the chimpanzee at the second, seventh and ninth weeks after inoculation, and remained pos. up

to 25 wk. Liver biopsies at Weeks 18 and 19 revealed of mild inflammation. Nucleotide sequence anal. of HCV recovered from the infected chimpanzee

at the second and ninth weeks showed 100% sequence homol. with the clone used

for **transfection** studies. Serum anti-HCV antibodies were not detected by EIA during the 25 wk follow-up period. These results suggest that i.v. administration of the virus-like particles derived from RNA-transfected HepG2 cells are infectious, and therefore, the pMO9.6-T7 clone is an infectious clone. These results provide new information that in vitro synthesized HCV particles produced from full-length HCV clone

can cause infection in a chimpanzee. This study will facilitate the use of innovative approaches to the study of assembly of HCV particles and mechanisms of virus infectivity in cell culture.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT

L10 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:338569 CAPLUS

DOCUMENT NUMBER: 133:276913

TITLE: Establishment of a controllable cell model with fusion gene of hepatitis C virus cDNA and luciferase reporter gene

AUTHOR(S): Lia, Zhansheng; Zhou, Yongxing; Jiao, Chengsong; Feng, Zhilua; Lian, Jianqi; Li, Jing; Li, Guangyu

CORPORATE SOURCE: Tangdu Hospital, Fourth Military Medical University, Xi'an, 710038, Peop. Rep. China

SOURCE: Zhonghua Weishengwuxue He Mianyixue Zazhi (2000), 20(2), 167-169  
CODEN: ZWMZDP; ISSN: 0254-5101

PUBLISHER: Weishenbu Beijing Shengwu Zhipin Yanjiuso

DOCUMENT TYPE: Journal

LANGUAGE: Chinese

AB Objective: To establish HCV cell culture model which is easy to measure. Methods: Controllable retroviral vector with fusion gene of hepatitis C virus (HCV) cDNA and luciferase (luc) reporter gene was constructed by mol. cloning technique, the transfection of this retroviral vector in a human hepatic carcinoma cell (HHCC) line was performed by lipofectAMINE and then luciferase activity in the cellular lysate was measured by scintillation counter. Results: (1) Fusion gene of the HCV 5' NCR-C region and luciferase reporter gene identified by restriction endonuclease cleavage have been cloned into pBPSIR1 vector. (2) The luciferase activity could maintain up to 20 days at least, and could be increased by puromycin treatment and regulated by tetracycline. Conclusion: A cell model for expression of HCV C-E1 and luciferase genes was established for gene therapy studies against HCV C-E1 sequences.

L10 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:698700 CAPLUS

DOCUMENT NUMBER: 125:324868

TITLE: In vivo transfection of rat liver with hepatitis C virus cDNA using cationic liposome-mediated gene delivery

AUTHOR(S): Hayashi, Norio; Takehara, Tetsuo; Kamada, Takenobu

CORPORATE SOURCE: School Medicine, Osaka University, Osaka, 565, Japan

SOURCE: Proceedings of the International Symposium of the Princess Takamatsu Cancer Research Fund (1995), Volume Date 1994, 25th(Hepatitis C Virus and Its Involvement in the Development of Hepatocellular Carcinoma), 143-149  
CODEN: PPTCBY

PUBLISHER: Princeton Scientific

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The lack of a small animal model for hepatitis C virus (HCV) infection has impeded elucidation of the pathogenesis of this virus. The aim of this study was to develop an HCV-expressing animal model using cationic liposome-mediated in vivo gene transfer. To examine the feasibility of this strategy, an expression vector composed of the LacZ gene driven by the .beta.-actin promoter, pActLacZ, was injected retrogradely into the common bile ducts of adult rats. X-Gal histochem. staining clearly showed that the LacZ gene was expressed in hepatocytes. Maximal expression was obsd. at a DNA:lipofectin ratio of 1:4. Based on this observation, an

expression vector contg. the full-length of HCV cDNA, pAGS3M091, was evaluated in adult rats. Two days after intrabiliary administration of pAGS3M091, PCR amplification of reverse-transcribed liver RNA demonstrated the 5' and 3' portions of HCV transcripts derived from pAGS3M091. Immunohistochem. anal. revealed the HCV core protein in

a

small no. of hepatocytes scattered in the lobules. Thus, the full-length of the HCV genome was successfully expressed in adult rat liver using liposome-mediated in vivo gene transfer.

L10 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:271824 CAPLUS

DOCUMENT NUMBER: 122:76311

TITLE: Transfection of a differentiated human hepatoma cell line (Huh7) with in vitro-transcribed hepatitis C virus (HCV) RNA and establishment of a long-term culture persistently infected with HCV

AUTHOR(S): Yoo, Byoung J.; Selby, Mark J.; Choe, Joonho; Suh, Byung S.; Choi, Steven H.; Joh, Jean S.; Nuovo,

Gerald

J.; Lee, Hyo-Suk; Houghton, Michael; Han, Jang H.  
CORPORATE SOURCE: Chiron Corp., Emeryville, CA, 94608, USA

SOURCE: Journal of Virology (1995), 69(1), 32-8

CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB T7 RNA polymerase transcripts of a putative full-length cDNA clone of hepatitis C virus type 1 (HCV-1) were used to transfect a differentiated human hepatoma cell line, Huh7. The transfected genome replicated in cells, as evidenced by the appearance of progeny HCV RNA, detection of neg.-strand viral RNA, and incorporation of [3H]uridine into the viral genome. Incubation of naive Huh7 cells with conditioned medium from transfected cells resulted in a new HCV infection, suggesting the prodn. of biol. active virus in the inoculum. Maintenance of the transfected cells under serum-free culture conditions resulted in the selection of persistently infected cells which displayed a distinctive cellular morphol. This is the first demonstration that HCV RNA produced from cloned HCV cDNA is infectious and replication competent. This approach should provide a valuable system for studying HCV replication, persistence, and pathogenicity.

L10 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1993:535163 CAPLUS

DOCUMENT NUMBER: 119:135163

TITLE: Expression, identification and subcellular localization of the proteins encoded by the hepatitis C viral genome

AUTHOR(S): Selby, Mark J.; Choo, Qui Lim; Berger, Kim; Kuo, George; Glazer, Edward; Eckart, Michael; Lee, Cindy; Chien, David; Kuo, Carol; Houghton, Michael

CORPORATE SOURCE: Chiron corp., Emeryville, CA, 94608, USA

SOURCE: Journal of General Virology (1993), 74(6), 1103-13

CODEN: JGVIAY; ISSN: 0022-1317

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors expressed the full-length coding region and selected domains of the hepatitis C virus (HCV) cDNA in mammalian cells by transfection. Using HCV antibody-pos. human sera and monospecific antibodies the proteins encoded by the putative structural

and nonstructural regions of the open reading frame of HCV were identified as core (p22), E1 (gp32-35), E2 (gp68-72), NS2 (p23), NS3 (p72), NS4a and b (p10 and p27) and NS5a and b (p56 and p70). The authors also defined the subcellular localizations of the HCV proteins using indirect immunofluorescence assays.

=> DIS L8 1- IBIB ABS

YOU HAVE REQUESTED DATA FROM 3 ANSWERS - CONTINUE? Y/(N):Y  
THE ESTIMATED COST FOR THIS REQUEST IS 7.25 U.S. DOLLARS  
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L8 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:407405 CAPLUS  
TITLE: The effect of ribavirin and IMPDH inhibitors on hepatitis C virus subgenomic replicon RNA  
AUTHOR(S): Zhou, Sifang; Liu, Rong; Baroudy, Bahige M.; Malcolm, Bruce A.; Reyes, Gregory R.  
CORPORATE SOURCE: Antiviral Therapy, Schering-Plough Research Institute,  
Kenilworth, NJ, 07033, USA  
SOURCE: Virology (2003), 310(2), 333-342  
CODEN: VIRLAX; ISSN: 0042-6822  
PUBLISHER: Academic Press  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The recent development of in vitro hepatitis C virus (HCV) RNA replication

systems has provided useful tools for studying the intracellular anti-HCV activity of ribavirin. Ribavirin has been shown to: (1) induce "error catastrophe" in poliovirus, Proc. Natl. Acad. Sci. USA 98, 6895-6900), (2) be a pseudo-substrate of the HCV RNA-dependent RNA polymerase (RdRp) in vitro, J. Biol. Chem. 276, 46094-46098), and (3) increase mutations in HCV RNA in the binary T7 polymerase/HCV cDNA replication system, J. Virol. 76, 8505-8517). These findings have led to the hypothesis that ribavirin may also induce error catastrophe in HCV. However, the functional relevance of ribavirin-induced HCV RNA

mutagenesis

is unclear. By use of a colony formation assay, in which RNA is isolated from the HCV subgenomic replicon system following treatment, the impact

of

ribavirin, inosine-5'-monophosphate dehydrogenase (IMPDH) inhibitors, and the combination was assessed. Ribavirin reduced HCV replicon colony-forming efficiency (CFE) in a dose-dependent fashion, suggesting that ribavirin may be misincorporated into replicon RNA and result in an anti-replicon effect analogous to error catastrophe. This effect was markedly suppressed by addn. of exogenous guanosine. Combination treatment with ribavirin and mycophenolic acid (MPA) or VX-497, both potent, nonnucleoside IMPDH inhibitors, led to a greatly enhanced anti-replicon effect. This enhancement was reversed by

inclusion

of guanosine with the treatment. In contrast, MPA or VX-497 alone had only marginal effects on both the quantity and quality (CFE) of replicon RNA, suggesting that although IMPDH inhibition is an important contributing factor to the overall ribavirin anti-HCV replicon activity, IMPDH inhibition by itself is not sufficient to exert an anti-HCV effect. Sequencing data targeting the neo gene segment of the HCV replicon indicated that ribavirin together with MPA or VX-497 increased the replicon error rate by about two-fold.

Taken together these results further suggest that lethal mutagenesis may be an effective anti-HCV strategy. The colony formation assay provides a useful tool for evaluating mutagenic nucleoside analogs for HCV therapy. Finally, the data from combination treatment indicate potential therapeutic value for an enhanced anti-HCV effect when using ribavirin in combination with IMPDH inhibition.

L8 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:401432 CAPLUS

TITLE: Gene expression associated with interferon alfa  
antiviral activity in an HCV  
replicon cell line

AUTHOR(S): Zhu, Haizhen; Zhao, Hongshan; Collins, Christin D.;  
Eckenrode, Sarah E.; Run, Qingguo; McIndoe, Richard  
A.; Crawford, James M.; Nelson, David R.; She,  
Jin-Xiong; Liu, Chen

CORPORATE SOURCE: Department of Pathology, Immunology, Laboratory  
Medicine, University of Florida College of Medicine,  
Gainesville, FL, USA

SOURCE: Hepatology (Philadelphia, PA, United States) (2003),  
37(5), 1180-1188

CODEN: HPTLD9; ISSN: 0270-9139

PUBLISHER: W. B. Saunders Co.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Interferon alfa (IFN-.alpha.)-based treatment is the only therapeutic  
option for chronic hepatitis C viral infection. However, the mol.  
mechanisms of IFN-.alpha. antiviral activity are not completely  
understood. The recent development of an HCV replicon  
cell culture system provides a feasible exptl. model to investigate the  
mol. details of IFN-induced direct antiviral activity in hepatocytes. In  
this report, we show that IFN-.alpha. can effectively inhibit HCV  
subgenomic RNA replication and suppress viral nonstructural protein  
synthesis. Using cDNA microarray anal., we also show that the  
replicon cells have different gene expression profile compared with the  
parental hepatoma cells (Huh7). IFN-.alpha. can induce a no. of  
responsive genes in the replicon cells. One of the genes, 6-16 (G1P3),  
can enhance IFN-.alpha. antiviral efficacy. In addn., we demonstrate  
that

IFN-.alpha. can significantly activate STAT3 in hepatoma cells,  
suggesting  
that this pathway plays a role in IFN-.alpha. signaling. In conclusion,  
our results indicate that IFN-.alpha. antiviral activity is assocd. with  
activation of STAT3-signaling pathway and intracellular gene activation.  
Our results also suggest that IFN-.alpha.-induced target genes may play  
an  
important role in IFN-.alpha. anti-HCV activity.

L8 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1997:276444 CAPLUS

DOCUMENT NUMBER: 126:248757

TITLE: Novel 3' terminal sequences of hepatitis C virus RNA  
and their use in the generation of infectious virus  
for diagnostic and therapeutic use

INVENTOR(S): Rice, Charles Iii; Kolykhalov, Alexander A.

PATENT ASSIGNEE(S): Washington University, USA

SOURCE: PCT Int. Appl., 58 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9708310	A1	19970306	WO 1996-US14033	19960828
W: AL, AU, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KP, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5874565	A	19990223	US 1995-520678	19950829
CA 2230452	AA	19970306	CA 1996-2230452	19960828
AU 9669097	A1	19970319	AU 1996-69097	19960828
AU 713112	B2	19991125		
EP 856051	A1	19980805	EP 1996-929843	19960828
EP 856051	B1	20020403		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
BR 9610307	A	19990706	BR 1996-10307	19960828
JP 11514241	T2	19991207	JP 1997-510618	19960828
ES 2174097	T3	20021101	ES 1996-929843	19960828
US 6297003	B1	20011002	US 1997-897126	19970718
US 2003017586	A1	20030123	US 2001-880567	20010613
US 2003027130	A1	20030206	US 2001-880508	20010613
US 2003054341	A1	20030320	US 2002-158314	20020530
PRIORITY APPLN. INFO.:			US 1995-520678	A 19950829
			WO 1996-US14033	W 19960828
			US 1997-897126	A1 19970718
			US 1999-368958	A1 19990805
AB Novel RNA sequences found at the 3' terminus of hepatitis C virus (HCV)				
RNA are characterized for diagnostic and therapeutic use. These sequences				
are strongly conserved amongst isolates and so are useful for nucleic-acid				
based diagnostics and for developing and evaluating novel anti-HCV therapies. This sequence element is likely to be essential for viral replication, and required for construction of full-length HCV cDNA clones capable of yielding infectious RNA, progeny virus or replication-competent HCV replicons. Such functional clones are useful tools for evaluation of therapeutic approaches and as substrates for developing candidate attenuated or inactivated HCV derivs. for vaccination against HCV. These 3' sequences form a stable hairpin loop that is essential for viral replication. The homopolymer tract that was believed to be the 3'-terminus of the virus is note essential for replication.				

=> DIS L7 1- IBIB ABS

YOU HAVE REQUESTED DATA FROM 14 ANSWERS - CONTINUE? Y/(N):Y  
THE ESTIMATED COST FOR THIS REQUEST IS 33.81 U.S. DOLLARS  
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L7 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:366153 CAPLUS

TITLE: The Hepatitis C Virus Non-structural NS5A Protein Inhibits Activating Protein-1 Function by Perturbing Ras-ERK Pathway Signaling

AUTHOR(S): Macdonald, Andrew; Crowder, Katherine; Street, Andrew;



CORPORATE SOURCE: McCormick, Christopher; Saksela, Kalle; Harris, Mark  
 Division School of Biochemistry and Molecular Biology,  
 of Microbiology, University of Leeds, Leeds, LS2 9JT,  
 UK  
 SOURCE: Journal of Biological Chemistry (2003), 278(20),  
 17775-17784  
 CODEN: JBCHA3; ISSN: 0021-9258  
 PUBLISHER: American Society for Biochemistry and Molecular  
 Biology  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The hepatitis C virus nonstructural 5A (NS5A) protein is a pleiotropic  
 phosphoprotein that has been shown to assoc. with a wide variety of  
 cellular signaling proteins. Of particular interest is the observation  
 that a highly conserved C-terminal Class II polyproline motif within NS5A  
 mediated assocn. with the Src homol. 3 domains of members of the Src  
 family of tyrosine kinases and the mitogenic adaptor protein Grb2 (A.  
 Macdonald, K. Crowder, A. Street, C. McCormick, and M. Harris, submitted  
 for publication). In this study, we analyzed the consequences of NS5A  
 expression on mitogenic signaling pathways within a variety of cell

lines.

Utilizing a transient luciferase reporter system, we obsd. that NS5A  
 inhibited the activity of the mitogenic and stress-activated  
 transcription

factor activating protein-1 (AP1). This inhibition was dependent upon a  
 Class II polyproline motif within NS5A. Using a combination of dominant  
 active and neg. mutants of components of the MAPK signaling pathways,  
 selective inhibitors, together with immunoblotting with phospho-specific  
 and phosphorylation-independent antibodies, we detd. the signaling  
 pathways targeted by NS5A to inhibit AP1. These studies demonstrated

that

in both stable NS5A-expressing cells and Huh-7-derived  
 cells harboring subgenomic hepatitis C virus (HCV)  
 replicons, this inhibition was mediated through the ERK signaling  
 pathway. Importantly, a comparable inhibition of AP1 reporter activity  
 was obsd. in hepatocyte-derived cell lines transduced with a baculovirus  
 vector driving expression of full-length HCV polyprotein. In conclusion,  
 these data strongly suggest a role for the NS5A protein in the  
 perturbation of mitogenic signaling pathways in HCV-infected hepatocytes.

L7 . ANSWER 2 OF 14 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:202161 CAPLUS  
 TITLE: RNA interference blocks gene expression and RNA  
 synthesis from hepatitis C replicons propagated in  
 human liver cells  
 AUTHOR(S): Wilson, Joyce A.; Jayasena, Sumedha; Khvorova,  
 Anastasia; Sabatinos, Sarah; Rodrigue-Gervais, Ian  
 Gael; Arya, Sudha; Sarangi, Farida; Harris-Brandts,  
 Marees; Beaulieu, Sylvie; Richardson, Christopher D.  
 CORPORATE SOURCE: Ontario Cancer Institute, Toronto, ON, M5G 2C1, Can.  
 SOURCE: Proceedings of the National Academy of Sciences of  
 the United States of America (2003), 100(5), 2783-2788  
 CODEN: PNASA6; ISSN: 0027-8424  
 PUBLISHER: National Academy of Sciences  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB RNA interference represents an exciting new technol. that could have  
 therapeutic applications for the treatment of viral infections.  
 Hepatitis

C virus (HCV) is a major cause of chronic liver disease and affects >270 million individuals worldwide. The HCV genome is a single-stranded RNA that functions as both a mRNA and replication template, making it an attractive target for the study of RNA interference. Double-stranded small interfering RNA (siRNA) mols. designed to target the HCV genome were introduced through electroporation into a human hepatoma cell line (Huh-7) that contained an HCV subgenomic replicon. Two siRNAs dramatically reduced virus-specific protein expression and RNA synthesis to levels that were 90% less than those seen in cells treated with neg. control siRNAs. These same siRNAs protected naive Huh-7 cells from challenge with HCV replicon RNA. Treatment of cells with synthetic siRNA was effective >72 h, but the duration of RNA interference could be extended beyond 3 wk through stable expression of complementary strands of the interfering RNA by using a bicistronic expression vector. These results suggest that a gene-therapeutic approach with siRNA could ultimately be used to treat HCV.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L7 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:187409 CAPLUS

TITLE: Identification and characterization of amphiphysin II as a novel cellular interaction partner of the hepatitis C virus NS5A protein

AUTHOR(S): Zech, Birgit; Kurtenbach, Alexander; Krieger, Nicole; Strand, Dennis; Blencke, Stephanie; Morbitzer, Monika;

Salassidis, Kostas; Cotten, Matt; Wissing, Josef; Obert, Sabine; Bartenschlager, Ralf; Herget, Thomas; Daub, Henrik

CORPORATE SOURCE: Axxima Pharmaceuticals AG, Martinsried, 82152, Germany

SOURCE: Journal of General Virology (2003), 84(3), 555-560  
CODEN: JGVIAY; ISSN: 0022-1317

PUBLISHER: Society for General Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The hepatitis C virus (HCV) NS5A protein is highly phosphorylated by cellular protein kinases. To study how NS5A might be integrated in cellular kinase signalling, we isolated phosphoproteins from HuH-7 hepatoma cells that specifically interacted with recombinant NS5A protein. Subsequent mass spectrometry identified the adaptor protein

amphiphysin II as a novel interaction partner of NS5A. Mutational anal. revealed that complex formation is primarily mediated by a proline-rich region in the C-terminal part of NS5A, which interacts with the amphiphysin II Src homol. 3 domain. Importantly, we could further demonstrate specific co-pptn. and cellular co-localization of endogenous amphiphysin II with NS5A in HuH-7 cells carrying a persistently replicating subgenomic HCV replicon. Although the NS5A-amphiphysin II interaction appeared to be dispensable for replication of these HCV RNAs in cell culture, our results indicate that NS5A-amphiphysin II complex formation might be of physiol. relevance for the HCV life cycle.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L7 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:155830 CAPLUS

DOCUMENT NUMBER: 138:350603

TITLE: Interference of hepatitis C virus RNA replication by short interfering RNAs

AUTHOR(S): Kapadia, Sharookh B.; Brideau-Andersen, Amy; Chisari, Francis V.

CORPORATE SOURCE: Department of Molecular and Experimental Medicine, The

SOURCE: Scripps Research Institute, La Jolla, CA, 92037, USA  
Proceedings of the National Academy of Sciences of

United States of America (2003), 100(4), 2014-2018

CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Hepatitis C virus (HCV) infection is a major cause of chronic liver disease, which can lead to the development of liver cirrhosis and hepatocellular carcinoma. Current therapy of patients with chronic HCV infection includes treatment with IFN.alpha. in combination with ribavirin. Because most treated patients do not resolve the infection, alternative treatment is essential. RNA interference (RNAi) is a recently discovered antiviral mechanism present in plants and animals that induces double-stranded RNA degradn. Using a selectable subgenomic HCV replicon cell culture system, we have shown that RNAi can specifically inhibit HCV RNA replication and protein expression in Huh-7 cells that stably replicate the HCV genome, and that this antiviral effect is independent of IFN. These results suggest that RNAi may represent a new approach for the treatment of persistent

HCV infection.

REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L7 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:869928 CAPLUS

DOCUMENT NUMBER: 138:149120

TITLE: Cell-free replication of the hepatitis C virus subgenomic replicon

AUTHOR(S): Ali, Naushad; Tardif, Keith D.; Siddiqui, Aleem

CORPORATE SOURCE: Department of Microbiology and Program in Molecular Biology, University of Colorado Health Sciences Center, Denver, CO, 80262, USA

SOURCE: Journal of Virology (2002), 76(23), 12001-12007  
CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The hepatitis C virus (HCV) contains a plus-strand RNA genome. The 5' noncoding region (NCR) of the viral genome functions as an internal ribosome entry site, and its unique 3' NCR is required for the assembly of

the replication complex during initiation of HCV RNA replication.  
Lohmann

et al. (V. Lohmann, F. Korner, J.-O. Koch, U. Herian, L. Theilman, and R. Batenschlager, Science 285:110-113, 1999) developed a subgenomic **HCV replicon** system, which represents an important tool in studying HCV replication in cultured cells. In this study, we describe a cell-free replication system that utilizes cytoplasmic lysates prep'd. from Huh-7 cells harboring the HCV subgenomic replicons. These lysates, which contain ribonucleoprotein complexes assoc'd. with cellular membranes, were capable of incorporating [ $\alpha$ .32P]CTP into newly synthesized RNA from subgenomic replicons in vitro. Replicative forms (RFs) and replicative intermediates (RIs) were synthesized from the endogenous HCV RNA templates. Consistent with previous observations, RFs were found to be resistant to RNase A digestion, whereas RIs were sensitive to RNase treatment. The radiolabeled HCV RF-RI complexes contained both minus and plus strands and were specific to the lysates derived from replicon-expressing cells. The availability of a cell-free replication system offers opportunities to probe the mechanism(s) of HCV replication. It also provides a novel assay for potential therapeutic agents.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2002:575245 CAPLUS  
 DOCUMENT NUMBER: 137:136139  
 TITLE: Hepatitis C virus replicons and replicon enhanced cells  
 INVENTOR(S): De Francesco, Raffaele; Migliaccio, Giovanni; Paonessa, Giacomo  
 PATENT ASSIGNEE(S): Istituto Di Ricerche Di Biologia Molecolare P. Angeletti Spa, Italy  
 SOURCE: PCT Int. Appl., 69 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002059321	A2	20020801	WO 2002-EP526	20020116
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				

PRIORITY APPLN. INFO.: US 2001-263479P P 20010123  
 AB The present invention features hepatitis C virus (HCV) nucleic acids contg. one or more adaptive mutations, and **HCV replicon** enhanced cells. Adaptive mutations are mutations that enhance **HCV replicon** activity, and **HCV replicon** enhanced cells are cells having an increased ability to maintain an **HCV replicon**. Consensus mutations found in the Con1 HCV isolate cultured in Huh-7 cells are not randomly distributed bu are clustered in the regions coding for the NS5A protein (frequency 1 .times. 10<sup>-3</sup>) and for the NS3 protein (frequency 0.5 .times. 10<sup>-3</sup>); with the exception of 2 silent mutations found in NS5A AND NS5B, consensus mutations occurring in the NS region resulted in changes in the deduced

amino acid sequence. Preferred NS3 adaptive mutations include Gly1095Ala (g3625c), Glu1202Gly (a3946g), and Ala1347Thr (g4380a); preferred NS5A mutations include Lys inserted after position 2039 (aaa@6458), Asn2041Thr (a6463c), Ser2173Phe (c6859t), Ser2197Phe (c6931t), Leu2198Ser (t6934c), Ala2199Thr (g6936a), and Ser2204Arg (c6953a or c6953g). The detectable replication and expression of HCV RNA in a cell culture system has a variety of different uses including being used to study HCV replication and expression, to study HCV and host cell interactions, to product HCV RNA, to product HCV proteins, and to provide a system for measuring the ability of a compd. to modulate one or more HCV activities. Preferred cells for use with a **HCV replicon** are Huh-7 cells and Huh-7 derived cells produced by introducing one or more phenotypic and/or genotypic modifications.

L7 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:555962 CAPLUS

DOCUMENT NUMBER: 137:106475

TITLE: Efficient hepatitis C virus replicon and its use in identifying antiviral compounds

INVENTOR(S): Wimmer, Eckard; Liang, Chengyu; Jang, Sung Key; Hahm, Bumsuk

PATENT ASSIGNEE(S): USA.

SOURCE: U.S. Pat. Appl. Publ., 17 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002098202	A1	20020725	US 2001-998900	20011129

PRIORITY APPLN. INFO.: US 2001-998900 20011129

AB The present invention provides a hepatitis C virus (**HCV**) **replicon** that efficiently replicates in an eukaryotic cell. The **HCV replicon** includes a nucleic acid sequence encoding a subgenomic fragments of HCV of any genotype that confer on the RNA the ability to replicate, and a nucleic acid sequence encoding an acetyl transferase selectable marker, such as puromycin. Also provided is an

**HCV** type 1a replicon that efficiently replicates in an eukaryotic cell and includes a nucleic acid sequence encoding subgenomic fragments of type 1a HCV that confer on the RNA the ability to replicate, and a nucleic acid sequence encoding a acetyl transferase selectable marker. Further provided are eukaryotic cell lines that include an **HCV replicon** or an HCV type 1a replicon which efficiently replicate in the eukaryotic cell. The present invention also provides screening methods for identifying candidate compds. that inhibit the propagation of HCV.

L7 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:555629 CAPLUS

DOCUMENT NUMBER: 137:125359

TITLE: Preparation of nucleoside derivatives as inhibitors of

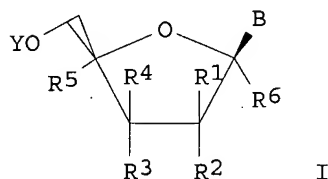
RNA-dependent RNA viral polymerase

INVENTOR(S): Carroll, Steven S.; Lafemina, Robert L.; Hall, Dawn L.; Himmelberger, Amy L.; Kuo, Lawrence C.; Maccoss, Malcolm; Olsen, David B.; Rutkowski, Carrie A.; Tomassini, Joanne E.; An, Haoyun; Bhat, Balkrishen;

Bhat, Neelima; Cook, Phillip Dan; Eldrup, Anne B.;  
Guinosso, Charles J.; Prhavic, Marija; Prakash, Thazha  
P.  
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; Isis Pharmaceuticals, Inc.  
SOURCE: PCT Int. Appl., 235 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 2  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002057425	A2	20020725	WO 2002-US1531	20020118
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ,				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002147160	A1	20021010	US 2002-52318	20020118
PRIORITY APPLN. INFO.:				
			US 2001-263313P	P 20010122
			US 2001-282069P	P 20010406
			US 2001-299320P	P 20010619
			US 2001-344528P	P 20011025

OTHER SOURCE(S): MARPAT 137:125359  
GI



AB The present invention provides the prepn. of nucleoside compds. I, wherein

B is nucleobase, Y is H, alkylcarbonyl, phosphate; R1 is H, alkenyl, alkynyl, alkyl; R2 and R3 are independently H, OH, halogen, alkyl, alkoxy, alkenyloxy, alkylthio, alkylcarbonyloxy, aryloxy, carbonyl, azido, amino, alkylamino; R4 and R5 together with the carbon atom to which they are attached form a 3- to 6-membered heterocycle; R4 is H, OH, SH, NH2, alkylamino, cycloalkylamino, halogen, alkyl, alkoxy, CF3; R5 and R6 are independently H, hydroxymethyl, Me, fluoromethyl; and certain derivs. thereof which are inhibitors of RNA-dependent RNA viral polymerase.

These

compds. are inhibitors of RNA-dependent RNA viral replication and are useful for the treatment of RNA-dependent RNA viral infection. They are particularly useful as inhibitors of hepatitis C virus (HCV) NS5B polymerase, as inhibitors of HCV replication, and/or for the treatment of hepatitis C infection. The invention also describes pharmaceutical

comps. contg. such nucleoside compds. alone or in combination with other agents active against RNA-dependent RNA viral infection, in particular

HCV

infection. Also disclosed are methods of inhibiting RNA-dependent RNA polymerase, inhibiting RNA-dependent RNA viral replication, and/or treating RNA-dependent RNA viral infection with the nucleoside compds. of the present invention. Thus, 4-amino-1-(2-C-methyl-.beta.-D-ribofuranosyl)-1H-pyrazolo[3,4-d]pyrimidine was prepd. as inhibitors of RNA-dependent RNA viral polymerase. Representative compds. tested in the HCV NS5B polymerase assay exhibited IC's less than 100 .mu.M. The compds.

of the present invention were also evaluated for their ability to affect the replication of Hepatitis C Virus RNA in cultured hepatoma (HuH-7) cells contg. a sub-genomic HCV Replicon.

L7 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:555511 CAPLUS

DOCUMENT NUMBER: 137:109450

TITLE: Preparation of nucleoside derivatives as inhibitors of

RNA-dependent RNA viral polymerase

INVENTOR(S): Carroll, Steven S.; Maccoss, Malcolm; Olsen, David B.;

Bhat, Balkrishen; Bhat, Neelima; Cook, Phillip Dan; Eldrup, Anne B.; Prakash, Thazha P.; Prhavc, Marija; Song, Quanlai

PATENT ASSIGNEE(S): Merck & Co., Inc., USA; Isis Pharmaceuticals, Inc.

SOURCE: PCT Int. Appl., 85 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002057287	A2	20020725	WO 2002-US3086	20020118
WO 2002057287	A3	20021010		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ,

TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002147160 A1 20021010 US 2002-52318 20020118

PRIORITY APPLN. INFO.:

US 2001-263313P P 20010122

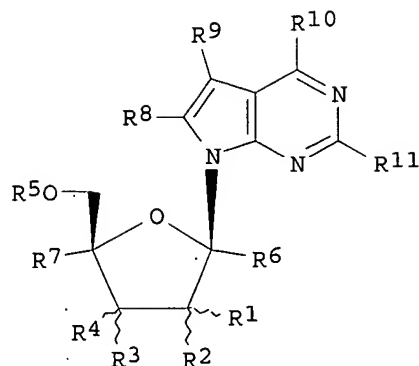
US 2001-282069P P 20010406

US 2001-299320P P 20010619

US 2001-344528P P 20011025

OTHER SOURCE(S): MARPAT 137:109450

GI



I

AB The present invention provides nucleoside compds. I, wherein R1 is alkenyl, alkynyl, alkyl, wherein alkyl is unsubstituted or substituted with hydroxy, amino, alkoxy, alkylthio, one to three fluorine atoms; R2 is hydrogen, fluorine, hydroxy, mercapto, alkoxy, alkyl; or R1 and R2 together with the carbon atom to which they are attached form a 3- to 6-membered satd. monocyclic ring system optionally contg. a heteroatom selected from O, S, and NC-alkyl; R3 and R4 are each independently hydrogen, cyano, azido, halogen, hydroxy, mercapto, amino, alkoxy, alkenyl, alkynyl, alkyl; R5 is hydrogen, alkylcarbonyl, phosphate; R6 and R7 are each independently hydrogen, Me, hydroxymethyl, or fluoromethyl;

R8 is hydrogen, alkyl, alkynyl, halogen, cyano, carboxy, alkyloxycarbonyl, azido, amino, alkylamino, di(alkyl)amino, hydroxy, alkoxy, alkylthio, alkylsulfonyl, alkylaminomethyl, cycloheteroalkyl; R9 is hydrogen, cyano, nitro, alkyl, NHCONH2, amide, thioamide, ester, C(=NH)NH2, hydroxy, alkoxy, amino, alkylamino, di(alkyl)amino, halogen, (1,3-oxazol-2-yl), (1,3-thiazol-2-yl), or (imidazol-2-yl); R10 and R11 are each independently hydrogen, hydroxy, halogen, alkoxy, amino, alkylamino, di(alkyl)amino, cycloalkylamino, di(cycloalkyl)amino, cycloheteroalkyl, and certain derivs. thereof which are inhibitors of RNA-dependent RNA viral polymerase. These compds. are inhibitors of RNA-dependent RNA viral replication and are useful for the treatment of RNA-dependent RNA viral infection. They are particularly useful as inhibitors of hepatitis C virus (HCV) NS5B polymerase, as inhibitors of HCV replication, and/or for the treatment of hepatitis C infection. The invention also describes pharmaceutical compns. contg. such nucleoside compds. alone or in combination with other agents active against RNA-dependent RNA viral infection, in particular HCV infection. Also disclosed are methods of inhibiting RNA-dependent RNA polymerase, inhibiting RNA-dependent RNA viral replication, and/or treating RNA-dependent RNA viral infection with the nucleoside compds. of the present invention. Thus, 4-amino-7-(2-C-methyl-.beta.-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine was prepd. as inhibitors of RNA-dependent RNA viral polymerase. Representative compds. tested in the HCV NS5B polymerase assay exhibited IC's less than 100 .mu.M. The nucleoside derivs. were also screened for cytotoxicity against cultured hepatoma (HuH-7) cells contg. a sub-genomic HCV Replicon in an MTS cell-based assay.



TITLE: Self-replicating RNA molecule from hepatitis C virus having adaptive mutations, and its uses in screening assay for HCV replication inhibitors

INVENTOR(S): Kukolj, George; Pause, Arnim

PATENT ASSIGNEE(S): Boehringer Ingelheim (Canada) Ltd., Can.

SOURCE: PCT Int. Appl., 140 pp.  
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002052015	A2	20020704	WO 2001-CA1843	20011220
<p>W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM</p> <p>RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG</p>				
US 2002142350	A1	20021003	US 2001-29907	20011221
PRIORITY APPLN. INFO.:			US 2000-257857P	P 20001222
<p>AB The present invention relates generally to a hepatitis C virus (HCV) RNA mol. that self-replicates in appropriate cell lines, particularly to a self-replicating HCV RNA construct having an enhanced efficiency of establishing cell culture replication. A unique HCV RNA mol. is provided having an enhanced efficiency of establishing cell culture replication. Novel adaptive mutations have been identified within the HCV non-structural region that improves the efficiency of establishing persistently replicating HCV RNA in cell culture. This self-replicating polynucleotide mol. contains, contrary to all previous reports, a 5'-NTR that can be either an A as an alternative to the G already disclosed and therefore provides an alternative to existing systems comprising a self-replicating HCV RNA mol. The G--&gt;A mutation gives rise to HCV RNA mols. that, in conjunction with mutations in the HCV non-structural region, such as the G(2042)C/R mutations, possess greater efficiency of transduction and/or replication. The HCV RNA encoding polyprotein comprising one or more amino acid substitution selected from the group consisting of: R(1135)K; S(1148)G; S(1560)G; K(1691)R; L(1701)F; I(1984)V; T(1993)A; G(2042)C; G(2042)R; S(2404)P; L(2155)P; P(2166)L; M(2992)T; and E(1202)G is claimed. These RNA mols. when transfected in a cell line are useful for evaluating potential inhibitors of HCV replication.</p>				
<p>L7 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2003 ACS</p> <p>ACCESSION NUMBER: 2002:375453 CAPLUS</p> <p>DOCUMENT NUMBER: 137:196537</p> <p>TITLE: Genetic analysis of sequences in the 3' nontranslated region of hepatitis C virus that are important for RNA replication</p> <p>AUTHOR(S): Friebe, Peter; Bartenschlager, Ralf</p> <p>CORPORATE SOURCE: Institute for Virology, Johannes Gutenberg University Mainz, Mainz, 55131, Germany</p> <p>SOURCE: Journal of Virology (2002), 76(11), 5326-5338 CODEN: JOVIAM; ISSN: 0022-538X</p>				

PUBLISHER: American Society for Microbiology  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The genome of the hepatitis C virus (HCV) is a plus-strand RNA mol. that carries a single long open reading frame. It is flanked at either end by highly conserved nontranslated regions (NTRs) that mediate crucial steps in the viral life cycle. The 3' NTR of HCV has a tripartite structure composed of an about 40-nucleotide variable region, a poly(U/UC) tract that has a heterogeneous length, and a highly conserved 98-nucleotide 3'-terminal sequence designated the X tail or 3'X. Conflicting data as

to

the role the sequences in the 3' NTR play in RNA replication have been reported. By using the HCV replicon system, which is based on the self-replication of subgenomic HCV RNAs in human hepatoma cell line Huh-7, we mapped in this study the sequences in the 3' NTR required for RNA replication. We found that a mutant with

a

complete deletion of the variable region is viable but that replication is

reduced significantly. Only replicons in which the poly(U/UC) tract was replaced by a homouridine stretch of at least 26 nucleotides were able to replicate, whereas RNAs with homopolymeric guanine, adenine, or cytosine sequences were inactive. Deletions of individual or all stem-loop structures in 3'X were not tolerated, demonstrating that this region is most crucial for efficient RNA replication. Finally, we found that none of these deletions or substitutions within the 3' NTR affected RNA stability or translation, demonstrating that the primary effect of the mutations was on RNA replication. These data represent the first

detailed

mapping of sequences in the 3' NTR assumed to act as a promoter for initiation of minus-strand RNA synthesis.

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L7 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:368681 CAPLUS

DOCUMENT NUMBER: 136:382850

TITLE: Recombinant hepatitis C virus characterized by high efficiency replication in cell lines

INVENTOR(S): Bichko, Vadim

PATENT ASSIGNEE(S): Anadys Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 85 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002038793	A2	20020516	WO 2001-US46350	20011102
WO 2002038793	C2	20030213		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,  
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002025895 A5 20020521 AU 2002-25895 20011102  
US 2002155133 A1 20021024 US 2001-5469 20011107

PRIORITY APPLN. INFO.: US 2000-245866P P 20001107  
WO 2001-US46350 W 20011102

AB The present invention relates to the recombinant hepatitis C virus (HCV)-derived nucleic acids and to stable rapidly growing cell clones derived from human hepatoma Huh-7 cell line and supporting high titer replication of said recombinant HCV nucleic acids. The subgenomic HCV replicons and cell clones of the instant invention represent the in vitro system of choice for studies of HCV propagation, anti-viral drug screening, and vaccine development. The invention also provides RNA sequence of HCV clones in which mutations occur in NS3, NS4A, NS5A genes. The invention also provides methods for detection of HCV infection using antibody.

L7 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:248529 CAPLUS

DOCUMENT NUMBER: 137:120564

TITLE: Persistent and transient replication of full-length hepatitis C virus genomes in cell culture

AUTHOR(S): Pietschmann, Thomas; Lohmann, Volker; Kaul, Artur; Krieger, Nicole; Rinck, Gabriele; Rutter, Gabriel; Strand, Dennis; Bartenschlager, Ralf

CORPORATE SOURCE: Institute for Virology, Johannes-Gutenberg University Mainz, Mainz, 55131, Germany

SOURCE: Journal of Virology (2002), 76(8), 4008-4021

CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The recently developed subgenomic hepatitis C virus (HCV) replicons were limited by the fact that the sequence encoding the structural proteins was missing. Therefore, important information about

a possible influence of these proteins on replication and pathogenesis and about the mechanism of virus formation could not be obtained. Taking advantage of three cell culture-adaptive mutations that enhance RNA replication synergistically, we generated selectable full-length HCV genomes that amplify to high levels in the human hepatoma cell line Huh-7 and can be stably propagated for more than 6 mo.

The structural proteins are efficiently expressed, with the viral glycoproteins E1 and E2 forming heterodimers which are stable under nondenaturing conditions. No disulfide-linked glycoprotein aggregates were obsd., suggesting that the envelope proteins fold productively. Electron microscopy studies indicate that cell lines harboring these full-length HCV RNAs contain lipid droplets. The majority of the core protein was found on the surfaces of these structures, whereas the glycoproteins appear to localize to the endoplasmic reticulum and cis-Golgi compartments. In agreement with this distribution, no endoglycosidase H-resistant forms of these proteins were detectable. In

a search for the prodn. of viral particles, we noticed that these cells release substantial amts. of nuclease-resistant HCV RNA-contg. structures with a buoyant d. of 1.04 to 1.1 g/mL in iodixanol gradients. The same observation was made in transient-replication assays using an authentic highly adapted full-length HCV genome that lacks heterologous sequences. However, the fact that comparable amts. of such RNA-contg. structures

were

found in the supernatant of cells carrying subgenomic replicons demonstrates a nonspecific release independent of the presence of the structural proteins. These results suggest that Huh-7 cells lack host cell factors that are important for virus particle assembly and/or release.

REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT

L7 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:251500 CAPLUS

DOCUMENT NUMBER: 135:18375

TITLE: Interferon-.alpha. inhibits hepatitis C virus subgenomic RNA replication by an MxA-independent pathway

AUTHOR(S): Frese, Michael; Pietschmann, Thomas; Moradpour, Darius; Haller, Otto; Bartenschlager, Ralf

CORPORATE SOURCE: Abteilung Virologie, Institut für Medizinische Mikrobiologie und Hygiene, Universität Freiburg, Freiburg, D-79104, Germany

SOURCE: Journal of General Virology (2001), 82(4), 723-733  
CODEN: JGVIAY; ISSN: 0022-1317

PUBLISHER: Society for General Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB. Hepatitis C virus (HCV) persists in the majority of infected individuals and is a major cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. Chronic hepatitis C is currently treated with interferon (IFN)-.alpha. or with a combination of IFN-.alpha. and ribavirin. The availability of an HCV replicon system allowed the investigation of the effects of IFN on genuine HCV

replication in cultured cells. It is shown here that IFN-.alpha. inhibits subgenomic HCV RNA replication in HuH-7 human hepatoma cells.

Immunofluorescence, Western blot, and Northern blot anal. revealed that levels of both HCV protein and replicon RNA were reduced after treatment with IFN-.alpha. in a dose-dependent manner. In further expts., it was investigated whether MxA plays a role in the inhibition of HCV. The human

MxA protein is an IFN-induced GTPase that has antiviral activity against various RNA viruses. However, HCV RNA replication was not affected in transfected HuH-7 cells that transiently overexpressed

MxA. Moreover, a dominant-neg. mutant of MxA did not interfere with the antiviral activity of IFN-.alpha. against HCV RNA replication. Thus, IFN-.alpha. inhibits HCV replicons via an MxA-independent pathway.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT

=> DIS L6 1- IBIB ABS

YOU HAVE REQUESTED DATA FROM 4 ANSWERS - CONTINUE? Y/(N):Y

THE ESTIMATED COST FOR THIS REQUEST IS 9.66 U.S. DOLLARS

DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L6 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:969892 CAPLUS

DOCUMENT NUMBER: 138:249449  
 TITLE: Subgenomic Hepatitis C Virus Replicons Inducing Expression of a Secreted Enzymatic Reporter Protein  
 AUTHOR(S): Yi, MinKyung; Bodola, Francis; Lemon, Stanley M.  
 CORPORATE SOURCE: Department of Microbiology and Immunology, The University of Texas Medical Branch at Galveston, Galveston, TX, 77555-1019, USA  
 SOURCE: Virology (2002), 304(2), 197-210  
 CODEN: VIRLAX; ISSN: 0042-6822  
 PUBLISHER: Elsevier Science  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB We constructed dicistronic, subgenomic hepatitis C virus (HCV) **replicons** in which the sequence encoding the human immunodeficiency virus (HIV) tat protein was placed in the upstream cistron, between the HCV 5'NTR and a picornaviral 2A proteinase sequence fused to the selectable marker Neo. Stably transformed Huh7 cells expressing secreted alk. phosphatase (SEAP) under transcriptional control of the HIV LTR promoter actively secreted SEAP following transfection with these replicon RNAs. Extracellular SEAP activity correlated closely with intracellular HCV RNA levels, as detd. by Northern blotting and real-time RT-PCR anal. These RNAs replicated efficiently despite the absence of core-protein-coding sequence downstream of the HCV IRES.. The replication efficiency of replicons derived from the HCV-N strain of HCV was significantly greater than those derived from Con1 in transiently transfected cells. Using this reporter system, we have demonstrated significant differences in the response to interferon .alpha.-2b in cell lines contg. replicons derived from these two strains of HCV.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L6 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:504935 CAPLUS  
 DOCUMENT NUMBER: 137:74392  
 TITLE: Self-replicating RNA molecule from hepatitis C virus having adaptive mutations, and its uses in screening assay for HCV replication inhibitors  
 INVENTOR(S): Kukolj, George; Pause, Arnim  
 PATENT ASSIGNEE(S): Boehringer Ingelheim (Canada) Ltd., Can.  
 SOURCE: PCT Int. Appl., 140 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002052015	A2	20020704	WO 2001-CA1843	20011220
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,				

CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,  
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002142350 A1 20021003 US 2001-29907 20011221

PRIORITY APPLN. INFO.: US 2000-257857P P 20001222

AB The present invention relates generally to a hepatitis C virus (HCV) RNA mol. that self-replicates in appropriate cell lines, particularly to a self-replicating HCV RNA construct having an enhanced efficiency of establishing cell culture replication. A unique HCV RNA mol. is provided having an enhanced efficiency of establishing cell culture replication. Novel adaptive mutations have been identified within the HCV non-structural region that improves the efficiency of establishing persistently replicating HCV RNA in cell culture. This self-replicating polynucleotide mol. contains, contrary to all previous reports, a 5'-NTR that can be either an A as an alternative to the G already disclosed and therefore provides an alternative to existing systems comprising a self-replicating HCV RNA mol. The G-->A mutation gives rise to HCV RNA mols. that, in conjunction with mutations in the HCV non-structural region, such as the G(2042)C/R mutations, possess greater efficiency of transduction and/or replication. The HCV RNA encoding polyprotein comprising one or more amino acid substitution selected from the group consisting of: R(1135)K; S(1148)G; S(1560)G; K(1691)R; L(1701)F; I(1984)V; T(1993)A; G(2042)C; G(2042)R; S(2404)P; L(2155)P; P(2166)L; M(2992)T; and E(1202)G is claimed. These RNA mols. when transfected in a cell line are useful for evaluating potential inhibitors of HCV replication.

L6 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:375453 CAPLUS

DOCUMENT NUMBER: 137:196537

TITLE: Genetic analysis of sequences in the 3' nontranslated region of hepatitis C virus that are important for

RNA

replication

AUTHOR(S): Friebe, Peter; Bartenschlager, Ralf

CORPORATE SOURCE: Institute for Virology, Johannes Gutenberg University Mainz, Mainz, 55131, Germany

SOURCE: Journal of Virology (2002), 76(11), 5326-5338

CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The genome of the hepatitis C virus (HCV) is a plus-strand RNA mol. that carries a single long open reading frame. It is flanked at either end by highly conserved nontranslated regions (NTRs) that mediate crucial steps in the viral life cycle. The 3' NTR of HCV has a tripartite structure composed of an about 40-nucleotide variable region,

a

poly(U/UC) tract that has a heterogeneous length, and a highly conserved 98-nucleotide 3'-terminal sequence designated the X tail or 3'X.

Conflicting data as to the role the sequences in the 3' NTR play in RNA replication have been reported. By using the HCV

replicon system, which is based on the self-replication of

subgenomic HCV RNAs in human hepatoma cell line Huh-7, we mapped in this study the sequences in the 3' NTR required for RNA replication.

We found that a mutant with a complete deletion of the variable region is viable but that replication is reduced significantly. Only replicons in which the poly(U/UC) tract was replaced by a homouridine stretch of at least 26 nucleotides were able to replicate, whereas RNAs with homopolymeric guanine, adenine, or cytosine sequences were inactive.

Deletions of individual or all stem-loop structures in 3'X were not tolerated, demonstrating that this region is most crucial for efficient RNA replication. Finally, we found that none of these deletions or substitutions within the 3' **NTR** affected RNA stability or translation, demonstrating that the primary effect of the mutations was

on

RNA replication. These data represent the first detailed mapping of sequences in the 3' **NTR** assumed to act as a promoter for initiation of minus-strand RNA synthesis.

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L6 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:888337 CAPLUS

DOCUMENT NUMBER: 136:335975

TITLE: Sequences in the 5' nontranslated region of hepatitis C virus required for RNA replication

AUTHOR(S): Friebe, Peter; Lohmann, Volker; Krieger, Nicole; Bartenschlager, Ralf

CORPORATE SOURCE: Institute for Virology, Johannes-Gutenberg University Mainz, Mainz, 55131, Germany

SOURCE: Journal of Virology (2001), 75(24), 12047-12057

CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Sequences in the 5' and 3' termini of plus-strand RNA viruses harbor cis-acting elements important for efficient translation and replication. In case of the hepatitis C virus (HCV), a plus-strand RNA virus of the family Flaviviridae, a 341-nucleotide-long nontranslated region (**NTR**) is located at the 5' end of the genome. This sequence contains an internal ribosome entry site (IRES) that is located

downstream

of an about 40-nucleotide-long sequence of unknown function. By using our

recently developed **HCV replicon** system, we mapped and characterized the sequences in the 5' **NTR** required for RNA replication. We show that deletions introduced into the 5' terminal 40 nucleotides abolished RNA replication but only moderately affected translation. By generating a series of replicons with HCV-poliovirus

(PV)

chimeric 5' **NTRs**, we could show that the first 125 nucleotides of the HCV genome are essential and sufficient for RNA replication. However, the efficiency could be tremendously increased upon the addn. of the complete HCV 5' **NTR**. These data show that (i) sequences upstream of the HCV IRES are essential for RNA replication; (ii) the

first

125 nucleotides of the HCV 5' **NTR** are sufficient for RNA replication, but such replicon mols. are severely impaired for multiplication, and (iii) high-level HCV replication requires sequences located within the IRES. These data provide the first identification of signals in the 5' **NTR** of HCV RNA essential for replication of this virus.

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

=> DIS L5 1- IBIB ABS

YOU HAVE REQUESTED DATA FROM 3 ANSWERS - CONTINUE? Y/(N):Y

THE ESTIMATED COST FOR THIS REQUEST IS 7.25 U.S. DOLLARS

DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L5 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:407405 CAPLUS

TITLE: The effect of ribavirin and IMPDH inhibitors on hepatitis C virus subgenomic replicon RNA

AUTHOR(S): Zhou, Sifang; Liu, Rong; Baroudy, Bahige M.; Malcolm, Bruce A.; Reyes, Gregory R.

CORPORATE SOURCE: Antiviral Therapy, Schering-Plough Research Institute,

Kenilworth, NJ, 07033, USA

SOURCE: Virology (2003), 310(2), 333-342

CODEN: VIRLAX; ISSN: 0042-6822

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The recent development of in vitro hepatitis C virus (HCV) RNA replication

systems has provided useful tools for studying the intracellular anti-HCV activity of ribavirin. Ribavirin has been shown to: (1) induce "error catastrophe" in poliovirus, Proc. Natl. Acad. Sci. USA 98, 6895-6900), (2) be a pseudo-substrate of the HCV RNA-dependent RNA polymerase (RdRp) in vitro, J. Biol. Chem. 276, 46094-46098), and (3) increase mutations in HCV RNA in the binary T7 polymerase/HCV cDNA replication system, J. Virol. 76, 8505-8517). These findings have led to the hypothesis that ribavirin may also induce error catastrophe in HCV. However, the functional relevance of ribavirin-induced HCV RNA mutagenesis is unclear. By use of a colony formation assay, in which RNA is isolated from the HCV subgenomic replicon system following treatment, the impact of ribavirin, inosine-5'-monophosphate dehydrogenase (IMPDH) inhibitors, and the combination was assessed. Ribavirin reduced HCV replicon colony-forming efficiency (CFE) in a dose-dependent fashion, suggesting that ribavirin may be misincorporated into replicon RNA and result in an anti-replicon effect analogous to error catastrophe. This effect was markedly suppressed by addn. of exogenous guanosine. Combination treatment with ribavirin and mycophenolic acid (MPA) or VX-497, both potent, nonnucleoside IMPDH inhibitors, led to a greatly enhanced anti-replicon effect. This enhancement was reversed by

inclusion

of guanosine with the treatment. In contrast, MPA or VX-497 alone had only marginal effects on both the quantity and quality (CFE) of replicon RNA, suggesting that although IMPDH inhibition is an important contributing factor to the overall ribavirin anti-HCV replicon activity, IMPDH inhibition by itself is not sufficient to exert an anti-HCV effect. Sequencing data targeting the neo gene segment of the HCV replicon indicated that ribavirin together with MPA or VX-497 increased the replicon error rate

by

about two-fold. Taken together these results further suggest that lethal mutagenesis may be an effective anti-HCV strategy. The colony formation assay provides a useful tool for evaluating mutagenic nucleoside analogs for HCV therapy. Finally, the data from combination treatment indicate potential therapeutic value for an enhanced anti-HCV effect when using ribavirin in combination with IMPDH inhibition.

L5 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS



ACCESSION NUMBER: 2003:147266 CAPLUS  
TITLE: Persistent replication of hepatitis C virus replicons  
expressing the .beta.-lactamase reporter in  
subpopulations of highly permissive Huh7 cells  
AUTHOR(S): Murray, Edward M.; Grobler, Jay A.; Markel, Eric J.;  
Pagnoni, Marco F.; Paonessa, Giacomo; Simon, Adam J.;  
Flores, Osvaldo A.  
CORPORATE SOURCE: Department of Biological Chemistry, Merck Research  
Laboratories, West Point, PA, 19486, USA  
SOURCE: Journal of Virology (2003), 77(5), 2928-2935  
CODEN: JOVIAM; ISSN: 0022-538X  
PUBLISHER: American Society for Microbiology  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Progress toward development of better therapies for the treatment of  
hepatitis C virus (HCV) infection has been hampered by poor understanding  
of HCV biol. and the lack of biol. assays suitable for drug screening.  
Here we describe a powerful HCV replication system that employs  
HCV replicons expressing the .beta.-lactamase reporter  
(bla replicons) and subpopulations of Huh7 cells that are more permissive  
(or "enhanced") to HCV replication than naive Huh7 cells. Enhanced cells  
represent a small fraction of permissive cells present among naive Huh7  
cells that is enriched during selection with replicons expressing the  
neomycin phosphotransferase gene (neo replicons). The level of  
permissiveness of cell lines harboring neo replicons can vary  
greatly, and the enhanced phenotype is usually revealed upon removal of  
the neo replicon with inhibitors of HCV replication. Replicon  
removal is responsible for increased permissiveness, since this effect  
could be reproduced either with alpha interferon or with an HCV NS5B  
inhibitor. Moreover, adaptive mutations present in the replicon genome  
used during selection do not influence the permissiveness of the  
resulting

enhanced-cell population, suggesting that the mechanisms governing the  
permissiveness of enhanced cells are independent from viral adaptation.  
Because the .beta.-lactamase reporter allows simultaneous quantitation of  
replicon-harboring cells and reporter activity, it was possible to  
investigate the relationship between genome replication activity and the  
frequency with which transfected genomes can establish persistent  
replication. Our study demonstrates that differences in the replication  
potential of the viral genome are manifested primarily in the frequency  
with which persistent replication is established but modestly affect the  
no. of replicons obsd. per replicon-harboring cell. Replicon copy no.

was

found to vary over a narrow range that may be defined by a minimal no.  
required for persistent maintenance and a max. that is limited by the  
availability of essential host factors.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR  
THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT

L5 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:969892 CAPLUS  
DOCUMENT NUMBER: 138:249449  
TITLE: Subgenomic Hepatitis C Virus Replicons Inducing  
Expression of a Secreted Enzymatic Reporter Protein  
AUTHOR(S): Yi, MinKyung; Bodola, Francis; Lemon, Stanley M.  
CORPORATE SOURCE: Department of Microbiology and Immunology, The  
University of Texas Medical Branch at Galveston,  
Galveston, TX, 77555-1019, USA

SOURCE: Virology (2002), 304(2), 197-210  
CODEN: VIRLAX; ISSN: 0042-6822  
PUBLISHER: Elsevier Science  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB We constructed dicistronic, subgenomic hepatitis C virus (HCV) replicons in which the sequence encoding the human immunodeficiency virus (HIV) tat protein was placed in the upstream cistron, between the HCV 5'NTR and a picornaviral 2A proteinase sequence fused to the selectable marker **Neo**. Stably transformed Huh7 cells expressing secreted alk. phosphatase (SEAP) under transcriptional control of the HIV LTR promoter actively secreted SEAP following transfection with these replicon RNAs. Extracellular SEAP activity correlated closely with intracellular HCV RNA levels, as detd. by

Northern blotting and real-time RT-PCR anal. These RNAs replicated efficiently despite the absence of core-protein-coding sequence downstream of the HCV IRES. The replication efficiency of replicons derived from the HCV-N strain of HCV was significantly greater than those derived from Con1 in transiently transfected cells. Using this reporter system, we have demonstrated significant differences in the response to interferon .alpha.-2b in cell lines contg. replicons derived from these two strains of HCV.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE  
FORMAT

=> DIS L4 1- IBIB ABS

YOU HAVE REQUESTED DATA FROM 5 ANSWERS - CONTINUE? Y/(N):Y  
THE ESTIMATED COST FOR THIS REQUEST IS 12.08 U.S. DOLLARS  
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L4 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:317064 CAPLUS  
TITLE: Hepatitis C virus E2 and NS5A region variability during sequential treatment with two interferon-.alpha. preparations  
AUTHOR(S): Mangoni, Emanuele Durante; Forton, Daniel M.; Ruggiero, Giuseppe; Karayiannis, Peter  
CORPORATE SOURCE: Department of Medicine A, Faculty of Medicine, Imperial College of Science, Technology and Medicine, St. Mary's Campus-QEQMW, London, UK  
SOURCE: Journal of Medical Virology (2003), 70(1), 62-73  
CODEN: JMVIDB; ISSN: 0146-6615  
PUBLISHER: Wiley-Liss, Inc.  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB To det. the pattern and significance of the HCV genetic heterogeneity before and during treatment with **recombinant**-2b or lymphoblastoid .alpha.-interferon, hypervariable region 1 (HVR-1) and NS5A quasispecies were characterised by cloning and sequencing in 12 HCV-1b-infected subjects. Patients were either responder-relapsers or non-responders to treatment. Extensive amino acid sequence anal. was applied to reveal the significance of HCV variation at key sites within HVR-1 and NS5A regions. Genetic complexity, genetic diversity, and the non-synonymous to synonymous substitution ratios of HVR-1 quasispecies decreased during treatment in responder-relapser patients only, and more

markedly so following lymphoblastoid .alpha.-interferon. In non-responders, the HVR-1 quasispecies broadened. Amino acids G406 and Q409, which represent a major viral epitope, were highly conserved throughout treatment. Responder-relapser patients had a higher mutation frequency in NS5A than non-responders. Lymphoblastoid .alpha.-interferon promoted the selection of intermediate Interferon Sensitivity Detg.

#### Region

(ISDR) sequences, whereas **recombinant**-2b .alpha.-interferon favored maintenance or selection of conserved ISDR sequences.

#### Variability

upstream of the ISDR was assocd. with treatment response, but the amino acid substitutions conferring higher replicative ability to in vitro **HCV replicons** were absent in in vivo isolates. In conclusion, the pattern of HVR-1 quasispecies evolution correlates with the clin. response, and the conservation of specific amino acids may be useful for immune targeting in vivo. In responder-relapser patients, the initial HVR-1 evolution resembles that found in sustained responders. Variability within the entire NS5A, as opposed to a single region (ISDR), may have a role in influencing .alpha.-interferon treatment outcome. A differential effect of different .alpha.-interferon preps. on HCV quasispecies kinetics may exist.

REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

#### FORMAT

L4 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:187409 CAPLUS

TITLE: Identification and characterization of amphiphysin II as a novel cellular interaction partner of the hepatitis C virus NS5A protein

AUTHOR(S): Zech, Birgit; Kurtenbach, Alexander; Krieger, Nicole; Strand, Dennis; Blencke, Stephanie; Morbitzer, Monika;

Salassidis, Kostas; Cotten, Matt; Wissing, Josef; Obert, Sabine; Bartenschlager, Ralf; Herget, Thomas; Daub, Henrik

CORPORATE SOURCE: Axxima Pharmaceuticals AG, Martinsried, 82152, Germany

SOURCE: Journal of General Virology (2003), 84(3), 555-560  
CODEN: JGVIAY; ISSN: 0022-1317

PUBLISHER: Society for General Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The hepatitis C virus (HCV) NS5A protein is highly phosphorylated by cellular protein kinases. To study how NS5A might be integrated in cellular kinase signalling, we isolated phosphoproteins from HuH-7 hepatoma cells that specifically interacted with **recombinant** NS5A protein. Subsequent mass spectrometry identified the adaptor protein

amphiphysin II as a novel interaction partner of NS5A. Mutational anal. revealed that complex formation is primarily mediated by a proline-rich region in the C-terminal part of NS5A, which interacts with the amphiphysin II Src homol. 3 domain. Importantly, we could further demonstrate specific co-pptn. and cellular co-localization of endogenous amphiphysin II with NS5A in HuH-7 cells carrying a persistently replicating subgenomic **HCV replicon**. Although the NS5A-amphiphysin II interaction appeared to be dispensable for replication

of these HCV RNAs in cell culture, our results indicate that

NS5A-amphiphysin II complex formation might be of physiol. relevance for the HCV life cycle.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L4 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:26945 CAPLUS

TITLE: Ribonucleoside analogue that blocks replication of bovine viral diarrhea and hepatitis C viruses in culture

AUTHOR(S): Stuyver, Lieven J.; Whitaker, Tony; McBrayer, Tamara R.; Hernandez-Santiago, Brenda I.; Lostia, Stefania; Tharnish, Phillip M.; Ramesh, Mangala; Chu, Chung K.; Jordan, Robert; Shi, Junxing; Rachakonda, Suguna; Watanabe, Kyoichi A.; Otto, Michael J.; Schinazi, Raymond F.

CORPORATE SOURCE: Pharmasset Inc., Tucker, GA, 30084, USA  
SOURCE: Antimicrobial Agents and Chemotherapy (2003), 47(1), 244-254

CODEN: AMACCQ; ISSN: 0066-4804

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A base-modified nucleoside analog, .beta.-D-N4-hydroxycytidine (NHC), was found to have antipestivirus and antihepacivirus activities. This compd. inhibited the prodn. of cytopathic bovine viral diarrhea virus (BVDV) RNA in a dose-dependant manner with a 90% effective concn. (EC90) of 5.4 .mu.M, an observation that was confirmed by virus yield assays (EC90 = 2 .mu.M). When tested for hepatitis C virus (HCV) replicon RNA redn. in Huh7 cells, NHC had an EC90 of 5 .mu.M on day 4. The HCV RNA redn. was incubation time and nucleoside concn. dependent. The in vitro antiviral effect of NHC was additive with recombinant alpha interferon-2a and could be prevented by the addn. of exogenous cytidine and uridine but not of other natural ribo- or 2'-deoxynucleosides. When HCV RNA replicon cells were cultured in the presence of increasing concns. of NHC (up to 40 .mu.M) for up to 45 cell passages, no resistant replicon was selected. Similarly, resistant BVDV could not be selected after 20 passages. NHC was phosphorylated to the triphosphate form in Huh7 cells, but in cell-free HCV NS5B assays, synthetic NHC-triphosphate (NHC-TP) did not inhibit the polymn. reaction. Instead, NHC-TP appeared to serve as a weak alternative substrate for the viral polymerase, thereby changing the mobility of the product in polyacrylamide electrophoresis gels. We speculate that incorporated nucleoside analogs with the capacity of changing the thermodyn. of regulatory secondary structures (with or without introducing mutations) may represent an important class of new antiviral agents for the treatment

of RNA virus infections, esp. HCV.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L4 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:764415 CAPLUS

TITLE: Identification and Biological Characterization of Heterocyclic Inhibitors of the Hepatitis C Virus RNA-dependent RNA Polymerase

AUTHOR(S) : Dhanak, Dashyant; Duffy, Kevin J.; Johnston, Victor K.; Lin-Goerke, Juili; Darcy, Michael; Shaw, Antony N.; Gu, Baohua; Silverman, Carol; Gates, Adam T.; Nonnemacher, Michael R.; Earnshaw, David L.; Casper, David J.; Kaura, Arun; Baker, Audrey; Greenwood, Cathy; Gutshall, Lester L.; Maley, Derrick; DelVecchio, Alfred; Macarron, Ricardo; Hofmann, Glenn A.; Alnoah, Zaid; Cheng, Hung-Yuan; Chan, George; Khandekar, Sanjay; Keenan, Richard M.; Sarisky,

Robert

T.  
CORPORATE SOURCE: Dep. Med. Chem., The Musculoskeletal, Microbial and Proliferative Dis. Cent. Excellence Drug Disc., Metab. Viral Dis. Cent. Excellence Drug Disc., GlaxoSmithKline Pharm., Collegeville, PA, 19426, USA  
SOURCE: Journal of Biological Chemistry (2002), 277(41), 38322-38327  
CODEN: JBCHA3; ISSN: 0021-9258  
PUBLISHER: American Society for Biochemistry and Molecular Biology  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The hepatitis C virus (HCV) NS5B protein encodes an RNA-dependent RNA polymerase (RdRp), the primary catalytic enzyme of the HCV replicase complex. We established a biochem. RNA synthesis assay, using purified **recombinant** NS5B lacking the C-terminal 21 amino acid residues, to identify potential polymerase inhibitors from a high throughput screen of the GlaxoSmithKline proprietary compd. collection. The benzo-1,2,4-thiadiazine compd. (I) was a potent, highly specific

inhibitor

of NS5B. This agent interacts directly with the viral polymerase and inhibits RNA synthesis in a manner noncompetitive with respect to GTP. Furthermore, in the absence of an in vitro-reconstituted HCV replicase assay employing viral and host proteins, the ability of compd. 1 to inhibit NS5B-directed viral RNA replication was detd. using the Huh7 cell-based HCV replicon system. I reduced viral RNA in replicon cells with an IC50 of .apprx.0.5 .mu.m, suggesting that the inhibitor was able to access the perinuclear membrane and inhibit the polymerase activity in the context of a replicase complex. Preliminary structure-activity studies on I led to the identification of a modified inhibitor (II), showing an improvement in both biochem. and cell-based potency. Lastly, data are presented suggesting that these compds. interfere with the formation of neg. and pos. strand progeny RNA by a similar mode of action. Investigations are ongoing to assess the potential utility of such agents in the treatment of chronic HCV disease.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L4 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:368681 CAPLUS

DOCUMENT NUMBER: 136:382850

TITLE: **Recombinant** hepatitis C virus characterized by high efficiency replication in cell lines

INVENTOR(S) : Bichko, Vadim

PATENT ASSIGNEE(S) : Anadys Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 85 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002038793	A2	20020516	WO 2001-US46350	20011102
WO 2002038793	C2	20030213		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
AU 2002025895	A5	20020521	AU 2002-25895	20011102
US 2002155133	A1	20021024	US 2001-5469	20011107
PRIORITY APPLN. INFO.:			US 2000-245866P	P 20001107
			WO 2001-US46350	W 20011102

AB The present invention relates to the **recombinant** hepatitis C virus (HCV)-derived nucleic acids and to stable rapidly growing cell clones derived from human hepatoma Huh-7 cell line and supporting high titer replication of said **recombinant** HCV nucleic acids. The subgenomic **HCV replicons** and cell clones of the instant invention represent the in vitro system of choice for studies of HCV propagation, anti-viral drug screening, and vaccine development. The invention also provides RNA sequence of HCV clones in which mutations occur in NS3, NS4A, NS5A genes. The invention also provides methods for detection of HCV infection using antibody.

=> DIS L3 1 IBIB ABS

THE ESTIMATED COST FOR THIS REQUEST IS 2.42 U.S. DOLLARS  
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:407405 CAPLUS

TITLE: The effect of ribavirin and IMPDH inhibitors on hepatitis C virus subgenomic replicon RNA

AUTHOR(S): Zhou, Sifang; Liu, Rong; Baroudy, Bahige M.; Malcolm, Bruce A.; Reyes, Gregory R.

CORPORATE SOURCE: Antiviral Therapy, Schering-Plough Research Institute,

SOURCE: Kenilworth, NJ, 07033, USA  
Virology (2003), 310(2), 333-342  
CODEN: VIRLAX; ISSN: 0042-6822

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The recent development of in vitro hepatitis C virus (HCV) RNA replication

systems has provided useful tools for studying the intracellular anti-HCV activity of ribavirin. Ribavirin has been shown to: (1) induce "error catastrophe" in poliovirus, Proc. Natl. Acad. Sci. USA 98, 6895-6900), (2) be a pseudo-substrate of the HCV RNA-dependent RNA polymerase (RdRp) in vitro, J. Biol. Chem. 276, 46094-46098), and (3) increase mutations in HCV RNA in the binary T7 polymerase/HCV cDNA replication system, J. Virol. 76, 8505-8517). These findings have led to the hypothesis that ribavirin may also induce error catastrophe in HCV.

However, the functional relevance of ribavirin-induced HCV RNA  
 mutagenesis  
 is unclear. By use of a colony formation assay, in which RNA is isolated  
 from the HCV subgenomic replicon system following treatment, the impact  
 of  
 ribavirin, inosine-5'-monophosphate dehydrogenase (IMPDH) inhibitors, and  
 the combination was assessed. Ribavirin reduced **HCV**  
**replicon** colony-forming efficiency (CFE) in a dose-dependent  
 fashion, suggesting that ribavirin may be misincorporated into replicon  
 RNA and result in an anti-replicon effect analogous to error catastrophe.  
 This effect was markedly suppressed by addn. of exogenous guanosine.  
 Combination treatment with ribavirin and mycophenolic acid (MPA) or  
 VX-497, both potent, nonnucleoside IMPDH inhibitors, led to a greatly  
 enhanced anti-replicon effect. This enhancement was reversed by  
 inclusion  
 of guanosine with the treatment. In contrast, MPA or VX-497 alone had  
 only marginal effects on both the quantity and quality (CFE) of replicon  
 RNA, suggesting that although IMPDH inhibition is an important  
 contributing factor to the overall ribavirin anti-**HCV**  
**replicon** activity, IMPDH inhibition by itself is not sufficient to  
 exert an anti-HCV effect. Sequencing data targeting the neo gene segment  
 of the **HCV replicon** indicated that ribavirin together  
 with MPA or VX-497 increased the replicon error rate by about two-fold.  
 Taken together these results further suggest that lethal mutagenesis may  
 be an effective anti-HCV strategy. The colony formation assay provides a  
 useful tool for evaluating mutagenic nucleoside analogs for HCV therapy.  
 Finally, the data from combination treatment indicate potential  
 therapeutic value for an enhanced anti-HCV effect when using ribavirin in  
 combination with IMPDH inhibition.

=> DIS L1 1- TI

YOU HAVE REQUESTED DATA FROM 43 ANSWERS - CONTINUE? Y/(N):Y  
 THE ESTIMATED COST FOR THIS REQUEST IS 13.09 U.S. DOLLARS  
 DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L1 ANSWER 1 OF 43 CAPLUS COPYRIGHT 2003 ACS

TI Gene expression profiling of the cellular transcriptional network  
 regulated by alpha/beta interferon and its partial attenuation by the  
 hepatitis C virus nonstructural 5A protein

L1 ANSWER 2 OF 43 CAPLUS COPYRIGHT 2003 ACS

TI The effect of ribavirin and IMPDH inhibitors on hepatitis C virus  
 subgenomic replicon RNA

L1 ANSWER 3 OF 43 CAPLUS COPYRIGHT 2003 ACS

TI Gene expression associated with interferon alfa antiviral activity in an  
**HCV replicon** cell line

L1 ANSWER 4 OF 43 CAPLUS COPYRIGHT 2003 ACS

TI Synergistic Antiviral Activity of Human Interferon Combinations in the  
 Hepatitis C Virus Replicon System

L1 ANSWER 5 OF 43 CAPLUS COPYRIGHT 2003 ACS

TI The Hepatitis C Virus Non-structural NS5A Protein Inhibits Activating  
 Protein-1 Function by Perturbing Ras-ERK Pathway Signaling

L1 ANSWER 6 OF 43 CAPLUS COPYRIGHT 2003 ACS

TI Identification of a Key Determinant of Hepatitis C Virus Cell Culture  
 Adaptation in Domain II of NS3 Helicase

- L1 ANSWER 7 OF 43 CAPLUS COPYRIGHT 2003 ACS  
 TI Modified apoptotic molecule (BID) reduces hepatitis C virus infection in mice with chimeric human livers
- L1 ANSWER 8 OF 43 CAPLUS COPYRIGHT 2003 ACS  
 TI Hepatitis C virus E2 and NS5A region variability during sequential treatment with two interferon-.alpha. preparations
- L1 ANSWER 9 OF 43 CAPLUS COPYRIGHT 2003 ACS  
 TI Cytoskeletal requirements for hepatitis C virus (HCV) RNA synthesis in the  
**HCV replicon** cell culture system
- L1 ANSWER 10 OF 43 CAPLUS COPYRIGHT 2003 ACS  
 TI Alpha interferon induces distinct translational control programs to suppress hepatitis C virus RNA replication
- L1 ANSWER 11 OF 43 CAPLUS COPYRIGHT 2003 ACS  
 TI RNA interference blocks gene expression and RNA synthesis from hepatitis C  
 replicons propagated in human liver cells
- L1 ANSWER 12 OF 43 CAPLUS COPYRIGHT 2003 ACS  
 TI Identification and characterization of amphiphysin II as a novel cellular interaction partner of the hepatitis C virus NS5A protein
- L1 ANSWER 13 OF 43 CAPLUS COPYRIGHT 2003 ACS  
 TI The regulation of hepatitis C virus (HCV) internal ribosome-entry site-mediated translation by **HCV replicons** and nonstructural proteins
- L1 ANSWER 14 OF 43 CAPLUS COPYRIGHT 2003 ACS  
 TI Interference of hepatitis C virus RNA replication by short interfering RNAs
- L1 ANSWER 15 OF 43 CAPLUS COPYRIGHT 2003 ACS  
 TI Role of the 5'-proximal stem-loop structure of the 5' untranslated region in replication and translation of hepatitis C virus RNA
- L1 ANSWER 16 OF 43 CAPLUS COPYRIGHT 2003 ACS  
 TI Persistent replication of hepatitis C virus replicons expressing the .beta.-lactamase reporter in subpopulations of highly permissive Huh7 cells
- L1 ANSWER 17 OF 43 CAPLUS COPYRIGHT 2003 ACS  
 TI Ribonucleoside analogue that blocks replication of bovine viral diarrhea and hepatitis C viruses in culture
- L1 ANSWER 18 OF 43 CAPLUS COPYRIGHT 2003 ACS  
 TI Expression system comprising rescue protein and **HCV replicon** for construction of Hepatitis C mouse model and uses in drug screening
- L1 ANSWER 19 OF 43 CAPLUS COPYRIGHT 2003 ACS  
 TI Preparation of amino acid-containing nucleoside phosphoramidates as HCV antiviral agents
- L1 ANSWER 20 OF 43 CAPLUS COPYRIGHT 2003 ACS  
 TI Gene-trap identification of host cell proteins required for hepatitis C



virus replication

- L1 ANSWER 21 OF 43 CAPLUS COPYRIGHT 2003 ACS  
TI Genomic analysis of the host response to hepatitis C virus infection
- L1 ANSWER 22 OF 43 CAPLUS COPYRIGHT 2003 ACS  
TI Subgenomic Hepatitis C Virus Replicons Inducing Expression of a Secreted Enzymatic Reporter Protein
- L1 ANSWER 23 OF 43 CAPLUS COPYRIGHT 2003 ACS  
TI Cell-free replication of the hepatitis C virus subgenomic replicon
- L1 ANSWER 24 OF 43 CAPLUS COPYRIGHT 2003 ACS  
TI Identification and Biological Characterization of Heterocyclic Inhibitors of the Hepatitis C Virus RNA-dependent RNA Polymerase
- L1 ANSWER 25 OF 43 CAPLUS COPYRIGHT 2003 ACS  
TI Hepatitis C virus genome - Genomic structure and HCV replicon system
- L1 ANSWER 26 OF 43 CAPLUS COPYRIGHT 2003 ACS  
TI Nucleosides for HBV and HCV: Back to the future
- L1 ANSWER 27 OF 43 CAPLUS COPYRIGHT 2003 ACS  
TI Preparation of tripeptides as hepatitis C inhibitors
- L1 ANSWER 28 OF 43 CAPLUS COPYRIGHT 2003 ACS  
TI Hepatitis C virus replicons and replicon enhanced cells
- L1 ANSWER 29 OF 43 CAPLUS COPYRIGHT 2003 ACS  
TI Efficient hepatitis C virus replicon and its use in identifying antiviral compounds
- L1 ANSWER 30 OF 43 CAPLUS COPYRIGHT 2003 ACS  
TI Preparation of nucleoside derivatives as inhibitors of RNA-dependent RNA viral polymerase
- L1 ANSWER 31 OF 43 CAPLUS COPYRIGHT 2003 ACS  
TI Preparation of nucleoside derivatives as inhibitors of RNA-dependent RNA viral polymerase
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 TI Sequences in the 5' nontranslated region of hepatitis C virus required for RNA replication  
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 TI Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line  
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